PENDING CLAIMS

Following entry of this Amendment, claims 37-39, 42-49, 52-57, and 59-65 will be pending. Claims 37, 39, 45-49, and 52-57 have been amended. Claims 40, 41, 50, 51 and 58 have been cancelled. Claims 59-65 have been added. Support for claims 59, 60, 62 and 63 is found at page 15, line 21. Support for claims 61 and 64 is found at page 15, line 21 and at page 15, line 21 and page 19, line 23. Support for claim 65 is found at page 9, line 27 and at page 8, line 9 of serial no. 07/460,852, incorporated by reference herein (at page 1, line 19, and page 8, line 10).

SEQUENCE LISTING

The Examiner requires a new computer readable form containing the sequence listing in ASCII and correcting the number of amino acids listed for sequence 13. One is supplied herewith. A copy of the CRF Diskette Problem report is also enclosed.

35 U.S.C. §120

The Examiner states that disclosure with respect to glucagon or gamma amino decarboxylase is not entitled to the filing date of parent applications 07/460852 and 07/595936. Applicants do not acquiesce in this determination, but have not discussed it herein since no prior art rejection requires reliance on an earlier filing date.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37-58 stand rejected under 35 U.S.C. §112, first paragraph.

The Examiner notes that GAD is improperly defined as "gamma amino decarboxylase". Applicants submit that this as an apparent error, in view of the Wyborski reference cited at page 16, line 6 of the specification, and which is incorporated by reference. The Wyborski reference correctly defines GAD as glutamic acid decarboxylase. (A copy is enclosed.) Applicants also submit that the error is apparent in view of the fact, as noted by the Examiner, that "gamma amino decarboxylase" is not known to exist, while GAD has the conventional meaning attributed in, e.g., the Wyborski reference.

Applicants have amended the claims, and the specification at Table 1 on page 19, to correct the definition of "GAD".

The Examiner rejects claims related to glucagon and GAD for lack of enablement on the basis that the specification provides no specific guidance for obtaining those antigens or administering them to treat Type I diabetes. Applicants respectfully submit that one of ordinary skill in this art could have obtained both of those antigens without undue experimentation and could also have effectively administered them in view of the teachings in the specification and the knowledge in the art.

As stated in the Wyborski reference cited in the specification, "GAD from rat and mouse brain has been extensively purified in several laboratories" (citing five

references.) Thus, GAD appears to have been a readily available material. The Wyborski article also describes cDNA coding for GAD.

Glucagon was also a well known and readily available material, as shown by the Merck reference cited by the Examiner in a prior art rejection.

The specification provides guidelines for administration of bystander antigens in general (i.e., not limited to any particular bystander autoantigen). See page 16, line 31-page 18, line 2 concerning dosages and page 22, line 1-page 26, line 9 concerning formulations.

There is no evidence of record that administering glucagon or GAD involves particular difficulties that are not associated with administering, for example, insulin. It is unclear why undue experimentation would be required to administer glucagon or GAD to treat type I diabetes, but not insulin.

Also, applicants submit herewith a copy of Tian et al., NASAL ADMINISTRATION OF GLUTAMATE DECARBOXYLASE (GAD65) PEPTIDES INDUCES Th2 RESPONSES AND PREVENTS MURINE INSULIN-DEPENDENT DIABETES, *J. Exp. Med.*, 183:1561-1567 (1996), as confirmatory evidence that those skilled in the art can administer GAD according to the invention to treat type I diabetes. Tian et al. disclose successful suppression of autoimmune response associated with an *in vivo* model of type I diabetes: IDDM (insulin-dependent diabetes mellitus) in NOD (non-obese diabetic) mice. Specifically, GAD peptide was intranasally administered to such mice in an effective amount

in order to prevent IDDM. The authors found, in accordance with the present invention, that such administration results in antigen specific T-cell response that actively inhibits autoimmune disease progression (p. 1562, third paragraph).

The present specification itself provides evidence of the use of glucagon as a bystander antigen treating type I diabetes. Example 5 describes experiments in which 1 mg of glucagon was administered (twice weekly for five weeks) in the mouse model of type I diabetes, and found to suppress the disease. Specifically, such administration was found to decrease the incidence of insulitis. (As shown, e.g., in the Tian paper referenced above, the use of bystander antigen by nasal administration is also effective.)

The Examiner notes that the specification does not describe a length of time for administration. It is submitted to be apparent from the present specification that suppression of autoimmune response is an ongoing process that is not limited to administration of bystander antigen for a specific period, i.e., the treatment is administered for as long as there is a benefit.

The term "non-immunologically" is objected to as lacking support. Applicants respectfully disagree, but have deleted that term from the present claims.

In view of the amendment to the claims and the above discussion, applicants respectfully request that the Examiner withdraw the rejection of claims 37-58 under 35 U.S.C. §112, first paragraph.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 37-58 stand rejected under 35 U.S.C. §112, second paragraph on the basis that the term "non-immunologically" is indefinite. As discussed above, applicants have deleted this term from the claims.

Claims 45 and 55 stand rejected on the basis that "substantial" as used in those claims is indefinite. Applicants have deleted this term as well.

Claims 49-58 stand rejected on the basis that there is no antecedent basis for "inhalable dosage form". These claims have been amended to recite "pharmaceutical dosage form for nose or mouth administration". The word "inhalable" has been deleted.

REJECTION UNDER 35 U.S.C. §102

Claims 48-50 and 52-55 stand rejected under 35 U.S.C. §102(b) as anticipated by pages 1087-1088 of the Merck Manual. Applicants respectfully traverse this rejection.

Claims 48-50 and 52-55 recite a "pharmaceutical dosage form for nose or mouth administration". The Merck Manual describes a parenteral dosage form of glucagon. Specifically, the Manual describes a vial containing a glucagon powder, and describes a "diluting solution for parenteral administration". The combination of the two is disclosed as administered by subcutaneous means. There is, however, no disclosure of any dosage form that is adapted for nose or mouth administration as claimed.

Withdrawal of the rejection of claims 48-50 and 52-55 under 35 U.S.C. §102(b) as anticipated by the Merck Manual is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §103

Claims 37, 38, 40-45, 48, 49, 51-55, and 58 stand rejected under 35 U.S.C. §103 as obvious over Foster in view of Davydov et al. or Ecanow. The Examiner cites prior art relating to administration of autoantigens, but does not reject claims that recite administration of bystander antigens that are not autoantigens. Applicants have amended the rejected independent claims herein to recite that the "bystander antigen is not an autoantigen in said human." The claims have also been amended to exclude any insulin antigen (i.e., that embodiment of the invention as originally described is now deleted from the claims). As amended, the claims are non-obvious over the cited art.

Applicants have also amended the claims to delete recitation of the particular mechanism of action. Specifically, the claims no longer recite: "said antigen eliciting suppressor T-cells which cause the release of transforming growth factor beta (TGF-β) at a locus within the body of said human, wherein T cells contributing to autoimmune response are located, and thereby suppress the T-cells contributing to said response". It is submitted that the claims need not recite any mechanism by which the invention works so long as the elements are sufficiently set forth.

Withdrawal of the rejection of claims 37, 38, 40-45, 48, 49, 51-55, and 58 under 35 U.S.C. §103 as obvious over Foster in view of Davydov et al. or Ecanow is respectfully requested.

Claims 48-56 stand rejected under 35 U.S.C. §103 as obvious over the Merck Manual (p. 1087-1088) in view of Harvey. The Examiner cites Harvey for the proposition that it would have been obvious to form a dosage form for administration by routes such as the oral route. Applicants respectfully traverse this rejection.

As discussed above, the Merck manual only describes parenteral administration, in particularly subcutaneously. There is no suggestion, however, that administration by nose or mouth would have the required effect in treating diabetes that is disclosed. For example, it is clear from the Merck manual that glucagon is parenterally administered for "urgent" counteraction of hyperglycemia. There could have been no reasonable expectation of success, however, in view of the well known differences in effects in different routes of administration, that glucagon would be effective if orally or nasally administered. There is no teaching in any cited reference that glucagon would be absorbed sufficiently quickly, or at all, if administered by the route recited in the present claims.

In addition, the present invention relies on an entirely different way of treating diabetes, i.e., by suppression of autoimmune response. The incentive to administer glucagon by nose or mouth instead of parenterally comes from the present specification, which teaches the immunological benefits of doing so.

In sum, in the absence of the teachings of the present specification, one skilled in the art would not have been taught to make a dosage form containing glucagon for administration by nose or by mouth to treat type I diabetes, and in any case would not have had any reasonable expectation of success in doing so.

Withdrawal of the rejection of claims 48-56 under 35 U.S.C. §103 as obvious over the Merck Manual (p. 1087-1088) in view of Harvey is respectfully requested.

MAINTENANCE OF SEPARATE CLAIMS IN RELATED APPLICATIONS

The Action requires clear demarcation between the claims of the present application and those of serial nos. 08/461,591, 08/461,662, 08/468,996, 08/472,016, and 08/472,017.

Application serial no. 08/461,591 relates to oral or enteral administration of GAD to treat type I diabetes. The present application relates to administration by inhalation.

Application serial no. 08/461,662 relates to administration of bystander antigens by inhalation. The present application relates to administration by nose or by mouth.

Application serial no. 08/468,996 relates to oral or enteral administration of glucagon to treat type diabetes. The present application relates to administration by inhalation.

Application serial no. 08/472,016 relates to oral administration of insulin to treat or prevent type I diabetes. The present claims, as amended, relate to by inhalation administration of a bystander antigen to an individual in which that bystander antigen is not an autoantigen.

Application serial no. 08/472,017 relates to oral or enteral administration of bystander antigens. The present application relates to administration by inhalation.

The separate issue of double patenting, for example patentably indistinct overlapping coverage, is dealt with below.

DOUBLE PATENTING REJECTIONS

Claims 37-39, 41-45, 48, 49, and 51-55 stand rejected for obviousness-type double patenting over claims of U.S. Patent No. 5,399,347. The '347 patent relates to oral administration of type II collagen. The present method claims recite administration by nose or mouth of bystander antigens, and pharmaceutical inhalable dosage forms. The claims as amended exclude bystander antigens that are autoantigens in the treated human. Withdrawal of this provisional rejection is requested.

Claims 37, 38, 40, 42-45, 48, 49, and 51-55 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/419,502. The present claims, as amended, exclude bystander antigens that are autoantigens in the treated human. Withdrawal of this provisional rejection is requested.

Claims 37-58 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/328,562. The present claims, as amended, exclude bystander antigens that are autoantigens in the treated human. Withdrawal of this provisional rejection is requested.

Claims 37-58 stand provisionally rejected for obviousness-type double patenting over claims of application serial no. 08/279,275. The present claims, as amended, exclude bystander antigens that are autoantigens in the treated human. Withdrawal of this provisional rejection is requested.

Claims 37-58 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/427,016. The present claims, as amended, exclude bystander antigens that are autoantigens in the treated human. Withdrawal of this provisional rejection is requested.

Claims 37-58 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/472,017. Applicants intend to file an appropriate terminal disclaimer with respect to the '017 application if the '017 application issues before the present application does.

Claims 37-45, 47-55, and 57 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/461,591. Applicants intend to file an appropriate terminal disclaimer with respect to the '591 application if the '591 application issues before the present application does.

Claims 37-58 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/461,662. Applicants intend to file an appropriate terminal disclaimer with respect to the '662 application if the '662 application issues before the present application does.

Claims 37-46 and 48-56 stand provisionally rejected for obviousness-type double patenting over claims of serial no. 08/468,996. Applicants intend to file an appropriate terminal disclaimer with respect to the '996 application if the '996 application issues before the present application does.

CONCLUSION

It is submitted that the pending claims are now in condition for allowance. Issuance of a Notice to that effect is earnestly solicited.

Respectfully submitted,

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